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(21) International Application Number: PCT/GB99/02267 (22) International Filing Date: 14 July 1999 (14.07.99) (30) Priority Data: 98305596.3 14 July 1998 (14.07.98) EP (71) Applicant (for all designated States except US): THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY [CN/CN]; Clear Water Bay, Kowloon, Hong Kong (CN). (72) Inventors; and (75) Inventors/Applicants (for US only): HAYNES, Richard, Kingston [AU/CN]; The Hong Kong University of Science & Technology, House 2, 1 University Road, Clear Water Bay, Kowloon, Hong Kong (CN). CHAN, Ho-Wai [GB/CN]; Flat 15, 2/F, Kam Yung House, Kam Fung Court, Ma On Shan, Shatin, New Territories, Hong Kong (CN). LAM, Wai-Lun [GB/CN]; 6/F 100 Shantung Street, Mongkok, Kowloon, Hong Kong (CN). TSANG, Hing-Wo [GB/CN]; 20A To Shek Village, Sha Tin, New Territories, Hong Kong (CN). CHEUNG, Man-Ki [GB/CN]; Flat 4B Block 14, Laguna City, Cha Kwo Ling, Kowloon, Hong Kong (CN).		(74) Agent: WALLACE, Sheila, Jane; Lloyd Wise Tregear & Co., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)		
(57) Abstract This invention relates to the use of certain C-10 substituted derivatives of artemisinin of general formula (I) in the treatment and/or prophylaxis of diseases caused by infection with a parasite, certain novel C-10 substituted derivatives of artemisinin, processes for their preparation and pharmaceutical compositions containing such C-10 substituted derivatives. The compounds are particularly effective in the treatment of malaria, neosporosis and coccidiosis. <div data-bbox="909 1155 1299 1407"><chem>CC12C(C3C(C1)OC2C3C4C(C(C(C4)OC5C(C(C(C5)OC6C(C(C(C6)OC7C(C(C(C7)OC8C(C(C(C8)OC9C(C(C(C9)OC10C(C(C(C10)OC11C(C(C(C11)OC12C(C(C(C12)OC13C(C(C(C13)OC14C(C(C(C14)OC15C(C(C(C15)OC16C(C(C(C16)OC17C(C(C(C17)OC18C(C(C(C18)OC19C(C(C(C19)OC20C(C(C(C20)OC21C(C(C(C21)OC22C(C(C(C22)OC23C(C(C(C23)OC24C(C(C(C24)OC25C(C(C(C25)OC26C(C(C(C26)OC27C(C(C(C27)OC28C(C(C(C28)OC29C(C(C(C29)OC30C(C(C(C30)OC31C(C(C(C31)OC32C(C(C(C32)OC33C(C(C(C33)OC34C(C(C(C34)OC35C(C(C(C35)OC36C(C(C(C36)OC37C(C(C(C37)OC38C(C(C(C38)OC39C(C(C(C39)OC40C(C(C(C40)OC41C(C(C(C41)OC42C(C(C(C42)OC43C(C(C(C43)OC44C(C(C(C44)OC45C(C(C(C45)OC46C(C(C(C46)OC47C(C(C(C47)OC48C(C(C(C48)OC49C(C(C(C49)OC50C(C(C(C50)OC51C(C(C(C51)OC52C(C(C(C52)OC53C(C(C(C53)OC54C(C(C(C54)OC55C(C(C(C55)OC56C(C(C(C56)OC57C(C(C(C57)OC58C(C(C(C58)OC59C(C(C(C59)OC60C(C(C(C60)OC61C(C(C(C61)OC62C(C(C(C62)OC63C(C(C(C63)OC64C(C(C(C64)OC65C(C(C(C65)OC66C(C(C(C66)OC67C(C(C(C67)OC68C(C(C(C68)OC69C(C(C(C69)OC70C(C(C(C70)OC71C(C(C(C71)OC72C(C(C(C72)OC73C(C(C(C73)OC74C(C(C(C74)OC75C(C(C(C75)OC76C(C(C(C76)OC77C(C(C(C77)OC78C(C(C(C78)OC79C(C(C(C79)OC80C(C(C(C80)OC81C(C(C(C81)OC82C(C(C(C82)OC83C(C(C(C83)OC84C(C(C(C84)OC85C(C(C(C85)OC86C(C(C(C86)OC87C(C(C(C87)OC88C(C(C(C88)OC89C(C(C(C89)OC90C(C(C(C90)OC91C(C(C(C91)OC92C(C(C(C92)OC93C(C(C(C93)OC94C(C(C(C94)OC95C(C(C(C95)OC96C(C(C(C96)OC97C(C(C(C97)OC98C(C(C(C98)OC99C(C(C(C99)OC100C(C(C(C100)OC101C(C(C(C101)OC102C(C(C(C102)OC103C(C(C(C103)OC104C(C(C(C104)OC105C(C(C(C105)OC106C(C(C(C106)OC107C(C(C(C107)OC108C(C(C(C108)OC109C(C(C(C109)OC110C(C(C(C110)OC111C(C(C(C111)OC112C(C(C(C112)OC113C(C(C(C113)OC114C(C(C(C114)OC115C(C(C(C115)OC116C(C(C(C116)OC117C(C(C(C117)OC118C(C(C(C118)OC119C(C(C(C119)OC120C(C(C(C120)OC121C(C(C(C121)OC122C(C(C(C122)OC123C(C(C(C123)OC124C(C(C(C124)OC125C(C(C(C125)OC126C(C(C(C126)OC127C(C(C(C127)OC128C(C(C(C128)OC129C(C(C(C129)OC130C(C(C(C130)OC131C(C(C(C131)OC132C(C(C(C132)OC133C(C(C(C133)OC134C(C(C(C134)OC135C(C(C(C135)OC136C(C(C(C136)OC137C(C(C(C137)OC138C(C(C(C138)OC139C(C(C(C139)OC140C(C(C(C140)OC141C(C(C(C141)OC142C(C(C(C142)OC143C(C(C(C143)OC144C(C(C(C144)OC145C(C(C(C145)OC146C(C(C(C146)OC147C(C(C(C147)OC148C(C(C(C148)OC149C(C(C(C149)OC150C(C(C(C150)OC151C(C(C(C151)OC152C(C(C(C152)OC153C(C(C(C153)OC154C(C(C(C154)OC155C(C(C(C155)OC156C(C(C(C156)OC157C(C(C(C157)OC158C(C(C(C158)OC159C(C(C(C159)OC160C(C(C(C160)OC161C(C(C(C161)OC162C(C(C(C162)OC163C(C(C(C163)OC164C(C(C(C164)OC165C(C(C(C165)OC166C(C(C(C166)OC167C(C(C(C167)OC168C(C(C(C168)OC169C(C(C(C169)OC170C(C(C(C170)OC171C(C(C(C171)OC172C(C(C(C172)OC173C(C(C(C173)OC174C(C(C(C174)OC175C(C(C(C175)OC176C(C(C(C176)OC177C(C(C(C177)OC178C(C(C(C178)OC179C(C(C(C179)OC180C(C(C(C180)OC181C(C(C(C181)OC182C(C(C(C182)OC183C(C(C(C183)OC184C(C(C(C184)OC185C(C(C(C185)OC186C(C(C(C186)OC187C(C(C(C187)OC188C(C(C(C188)OC189C(C(C(C189)OC190C(C(C(C190)OC191C(C(C(C191)OC192C(C(C(C192)OC193C(C(C(C193)OC194C(C(C(C194)OC195C(C(C(C195)OC196C(C(C(C196)OC197C(C(C(C197)OC198C(C(C(C198)OC199C(C(C(C199)OC200C(C(C(C200)OC201C(C(C(C201)OC202C(C(C(C202)OC203C(C(C(C203)OC204C(C(C(C204)OC205C(C(C(C205)OC206C(C(C(C206)OC207C(C(C(C207)OC208C(C(C(C208)OC209C(C(C(C209)OC210C(C(C(C210)OC211C(C(C(C211)OC212C(C(C(C212)OC213C(C(C(C213)OC214C(C(C(C214)OC215C(C(C(C215)OC216C(C(C(C216)OC217C(C(C(C217)OC218C(C(C(C218)OC219C(C(C(C219)OC220C(C(C(C220)OC221C(C(C(C221)OC222C(C(C(C222)OC223C(C(C(C223)OC224C(C(C(C224)OC225C(C(C(C225)OC226C(C(C(C226)OC227C(C(C(C227)OC228C(C(C(C228)OC229C(C(C(C229)OC230C(C(C(C230)OC231C(C(C(C231)OC232C(C(C(C232)OC233C(C(C(C233)OC234C(C(C(C234)OC235C(C(C(C235)OC236C(C(C(C236)OC237C(C(C(C237)OC238C(C(C(C238)OC239C(C(C(C239)OC240C(C(C(C240)OC241C(C(C(C241)OC242C(C(C(C242)OC243C(C(C(C243)OC244C(C(C(C244)OC245C(C(C(C245)OC246C(C(C(C246)OC247C(C(C(C247)OC248C(C(C(C248)OC249C(C(C(C249)OC250C(C(C(C250)OC251C(C(C(C251)OC252C(C(C(C252)OC253C(C(C(C253)OC254C(C(C(C254)OC255C(C(C(C255)OC256C(C(C(C256)OC257C(C(C(C257)OC258C(C(C(C258)OC259C(C(C(C259)OC260C(C(C(C260)OC261C(C(C(C261)OC262C(C(C(C262)OC263C(C(C(C263)OC264C(C(C(C264)OC265C(C(C(C265)OC266C(C(C(C266)OC267C(C(C(C267)OC268C(C(C(C268)OC269C(C(C(C269)OC270C(C(C(C270)OC271C(C(C(C271)OC272C(C(C(C272)OC273C(C(C(C273)OC274C(C(C(C274)OC275C(C(C(C275)OC276C(C(C(C276)OC277C(C(C(C277)OC278C(C(C(C278)OC279C(C(C(C279)OC280C(C(C(C280)OC281C(C(C(C281)OC282C(C(C(C282)OC283C(C(C(C283)OC284C(C(C(C284)OC285C(C(C(C285)OC286C(C(C(C286)OC287C(C(C(C287)OC288C(C(C(C288)OC289C(C(C(C289)OC290C(C(C(C290)OC291C(C(C(C291)OC292C(C(C(C292)OC293C(C(C(C293)OC294C(C(C(C294)OC295C(C(C(C295)OC296C(C(C(C296)OC297C(C(C(C297)OC298C(C(C(C298)OC299C(C(C(C299)OC300C(C(C(C300)OC301C(C(C(C301)OC302C(C(C(C302)OC303C(C(C(C303)OC304C(C(C(C304)OC305C(C(C(C305)OC306C(C(C(C306)OC307C(C(C(C307)OC308C(C(C(C308)OC309C(C(C(C309)OC310C(C(C(C310)OC311C(C(C(C311)OC312C(C(C(C312)OC313C(C(C(C313)OC314C(C(C(C314)OC315C(C(C(C315)OC316C(C(C(C316)OC317C(C(C(C317)OC318C(C(C(C318)OC319C(C(C(C319)OC320C(C(C(C320)OC321C(C(C(C321)OC322C(C(C(C322)OC323C(C(C(C323)OC324C(C(C(C324)OC325C(C(C(C325)OC326C(C(C(C326)OC327C(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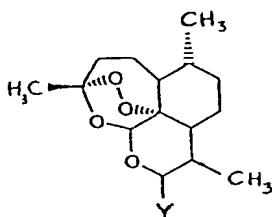
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CLAIMS

1. A compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclalkyl group or a group $-NR^1R^2$; where

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester;

for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium.

2. A compound according to claim 1 in which Y represents a halogen atom.

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3. A compound according to claim 1 or claim 2 in which Y represents a fluorine or bromine atom.

4. A compound according to claim 1 in which Y represents a C₃₋₈ cycloalkyl group, a C₆₋₁₈ aryl group, a 5- to 10-membered C-linked heteroaryl group or a 5- to 10-membered heterocyclyl-C₁₋₆ alkyl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, carboxyl, C₆₋₁₀ aryl, 5 to 10-membered heterocyclic and C₁₋₄ alkyl- or phenyl-substituted 5- to 10-membered heterocyclic groups.

5. A compound according to claim 4 in which Y represents a C₆₋₁₈ aryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino and carboxyl groups.

6. A compound according to claim 4 or claim 5 in which Y represents a phenyl, naphthyl, anthryl or phenanthryl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms and hydroxyl, methyl, vinyl, C₁₋₄ alkoxy and carboxyl groups.

7. A compound according to any one of claims 4 to 6 in which Y represents a phenyl, fluorophenyl, chlorophenyl, bromophenyl, trimethylphenyl, vinylphenyl, methoxyphenyl,

dimethoxyphenyl, trimethoxyphenyl, carboxylphenyl, naphthyl, hydroxynaphthyl, methoxynaphthyl, anthryl or phenanthryl group.

5 8. A compound according to any one of claims 4 to 7 in which Y represents a phenyl or trimethoxyphenyl group.

10 9. A compound according to claim 1 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl or C_{7-16} aralkyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 5- to 10-membered heterocyclic group or an amino group derived from a C_{1-6} alkyl ester of an amino acid, each
15 group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy carbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and
20 pyrimidinyl groups.

25 10. A compound according to claim 9 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-4} alkyl group and R^2 represents a C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 6- to 10-membered heterocyclic group or an amino group derived from a C_{1-4} alkyl ester of an amino acid, each
30 group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} haloalkyl, C_{1-4} alkoxy carbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

11. A compound according to claim 9 or claim 10 in which Y represents a propylamino, cyclopentylamino, cyclohexylamino, phenylamino, fluorophenylamino, chlorophenylamino, bromophenylamino, iodophenylamino, methoxycarbonylphenylamino, biphenylamino, benzylamino, 5 fluorobenzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino, diethylamino, morpholinyl, thiomorpholinyl, morpholinosulphonyl, indolinyl, tetrahydroisoquinolinyl, phenylpiperazinyl, fluorophenylpiperazinyl, 10 chlorophenylpiperazinyl, methylphenylpiperazinyl, trifluoromethylphenylpiperazinyl, methoxyphenylpiperazinyl, benzylpiperazinyl, pyridylpiperazinyl and pyrimidinylpiperazinyl group.

12. A compound according to any one of claims 9 to 11 in which Y represents a propylamino, phenylamino, bromophenylamino, iodophenylamino, biphenylamino, benzylamino, bis(trifluoromethyl)benzylamino, 20 phenylethylamino, phenyl-methoxycarbonylmethylamino or morpholinyl group.

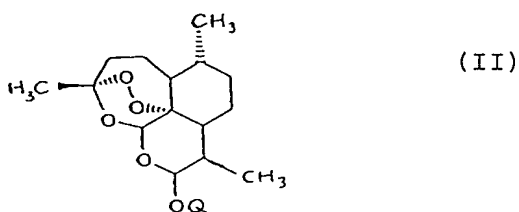
13. A compound according to any one of the preceding claims in which the parasite is an organism of the genus Neospora or the genus Eimeria. 25

14. Use of a compound of the general formula I as defined in any one of claims 1 to 12 for the manufacture of a medicament for the treatment and/or prophylaxis of a 30 disease caused by infection with a parasite other than an organism of the genus Plasmodium.

15. Use according to claim 14 in which the parasite is an organism of the genus Neospora or the genus Eimeria.

16. A compound of the general formula I as defined in any one of claims 1 to 12, with the proviso that, when Y is a group $-NR^1R^2$ and R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group, then R^1 is an optionally substituted alkyl group.

17. A process for the preparation of a compound of the general formula I according to claim 16 which comprises reacting a compound of the general formula II



20 in which Q represents a hydrogen atom or trimethylsilyl group, with a suitable halogenating agent to form a compound of the general formula I in which Y represents a halogen atom; and, if desired, reacting the compound of general formula I thus formed either with a Grignard reagent of the general formula $YMgX$ where Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclalkyl group and X is a halogen atom to form a compound of general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclalkyl group or with an

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amine of the general formula HNR^1R^2 where R^1 and R^2 are as defined in claim 13 to form a compound of general formula I in which Y represents a group $-\text{NR}^1\text{R}^2$ where R^1 and R^2 are as defined above.

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18. A process according to claim 17 in which a compound of the general formula I in which Y represents a bromine atom is generated in situ by reacting a compound of the general formula II in which Q represents a trimethylsilyl group with bromotrimethylsilane.

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19. A process for the preparation of a compound of the general formula I according to claim 16 in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclalkyl group which comprises reacting 9,10-anhydroartemisinin with a compound of the general formula Y-H, where Y is as defined above, in the presence of a suitable Lewis acid.

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20. A process for the preparation of a compound of the general formula I as defined in claim 1 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting 10-trichloroacetimidoyl-10-deoxoartemisinin with a compound of the general formula Y-H, where Y is defined above, in the presence of a suitable Lewis acid.

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21. A process according to claim 18 in which the 10-trichloroacetimidoyl-10-deoxoartemisinin is generated in situ by reacting a compound of formula II as defined in claim 17 in which Q represents a hydrogen atom with trichloroacetonitrile in the presence of a suitable base.

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22. A process for the preparation of a compound of the general formula I as defined in claim 1 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting a 10-acyloxyartemisinin compound in which the acyloxy group is of formula A-(C=O)-O-, where A represents an optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclic or polycyclic group, with a compound of the general formula Y-H, where Y is as defined above, in the presence of a Lewis acid.

23. A pharmaceutical composition which comprises a carrier and, as active ingredient, a compound of the general formula I according to claim 16.

24. A compound of the general formula I according to claim 16 for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium.

25. Use of a compound of the general formula I according to Claim 16 for the manufacture of a medicament for the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium.

26. A method for treating a disease caused by infection with a parasite other than an organism of the genus Plasmodium which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of the general formula I as defined in claim 1.

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27. A method for treating a disease caused by infection with a parasite of the genus Plasmodium which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of the general formula I according to claim 16.

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INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/GB 99/02267

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D493/18 A61K31/335 A61K31/35 //(C07D493/18,241:00), (C07D493/18,307:00),(C07D493/18,209:00),(C07D493/18,265:00), (C07D493/18,221:00) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFORD, C.W.: "Peroxidic Antimalarials" ADV. DRUG RES., vol. 29, 1997, pages 271-325, XP002119844 LONDON * see page 320, 2nd par., last sentence * the whole document	1-27
X	MESHNICK S R ET AL: "ARTEMISININ AND THE ANTIMALARIAL ENDOPEROXIDES: FROM HERBAL REMEDY TO TARGETED CHEMOTHERAPY" MICROBIOLOGICAL REVIEWS, vol. 60, no. 2, 1 June 1996 (1996-06-01), pages 301-315, XP002052313 * see page 306, right col., last par. * the whole document --- -/--	1-27
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *Z* document member of the same patent family		
Date of the actual completion of the international search 3 November 1999		Date of mailing of the international search report 30. 11. 99
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer Stellmach, J

INTERNATIONAL SEARCH REPORT

Int :ional Application No
PCT/GB 99/02267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 362 730 A (HOECHST AG) 11 April 1990 (1990-04-11) the whole document ----	1-27
Y	WO 93 08195 A (UNIV SYDNEY) 29 April 1993 (1993-04-29) the whole document ----	1-27
P,X	POSNER,G.H.: "Antimalarial peroxides in the quinghaosu (artesisimin) and yingzhaosu families" EXP.OPIN.THER.PATENTS, vol. 8, no. 11, November 1998 (1998-11), pages 1487-1493, XP002119814 LONDON the whole document ----	1-15,20
P,X	WO 99 33461 A (HAUSER INC ;UNIV JOHNS HOPKINS (US)) 8 July 1999 (1999-07-08) the whole document -----	1-27

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International Application No
PCT/GB 99/02267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	TONMUNPHEAN, S. ET AL.: "Comparative molecular field analysis of artemisinin derivatives: Ab initio versus semiempirical optimized structures " J.COMP.-AIDED MOL.DES., vol. 12, 1998, pages 397-409, XP002120343 AMSTERDAM	1-15, 20
X	* see p.402, fig. 2 * the whole document	16-25
X	LUO ET AL: "The Chemistry, Pharmacology, and Clinical Applications of Qinghaosu (Artemisinin) and Its Derivatives" MEDICINAL RESEARCH REVIEWS, vol. 7, no. 1, 1 January 1987 (1987-01-01), pages 29-57, XP002088809 ISSN: 0198-6325 the whole document	1-27
Y	YONG-HUA Y ET AL: "Artemisinin derivatives with 12-aniline substitution: synthesis and antimalarial activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 16, 17 August 1995 (1995-08-17), page 1791-1794 XP004135366 ISSN: 0960-894X the whole document	1-27
Y	PU ET AL: "Synthesis and Antimalarial Activities of Several Fluorinated Artemisinin Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 20, 1 January 1995 (1995-01-01), pages 4120-4124, XP002089611 ISSN: 0022-2623 the whole document	1-27
X	JUNG, M. ET AL.: "A Concise Synthesis of Novel Aromatic Analogs of Artemisinin" HETEROCYCLES, vol. 45, no. 6, 1997, pages 1055-1058, XP002120565 SENDAI the whole document	1-27
X	CN 1 122 806 A (SHANGHAI INST OF MATERIA MEDIC) 22 May 1996 (1996-05-22) the whole document	1-27
X	US 5 225 562 A (MCCHESNEY JAMES D ET AL) 6 July 1993 (1993-07-06) the whole document	1-27
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/02267

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Patent Application No
PCT/GB 99/02267

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